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Melding Regulatory, Pharmaceutical Industry, and U.S. Payer Perspectives on Improving Approaches to Heterogeneity of Treatment Effect in Research and Practice

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ABSTRACT

Effective pursuit of the science and management of heterogeneity of treatment effect (HTE) relies on the mutual understanding of the perspectives of, and collaboration among, the various stakeholders in health care. In this article, we compare, contrast, and endeavor to find areas of alignment across the perspectives of three such stakeholders — regulators, the biopharmaceutical and device industry, and U.S. payers. First, we discuss how evidence of HTE is generated and could be improved upon. For pharmaceuticals, much of the initial research is conducted by the pharmaceutical industry, guided by basic science but also delimited by potential markets, regulatory approval requirements, trial size considerations, and payer expectations for evidence of value. Once a drug is marketed, further evidence can be generated via combining trial data, conducting meta-analysis, and analyzing real-world results through observational research designs; we explore how these efforts can benefit from cooperation across these stakeholders. Second, we discuss the equally important utilization of HTE evidence so that physicians and patients have access to and can benefit from the learnings from this research. Research findings must be translated into actionable information and guidelines that can be incorporated into everyday practice. Doing so requires interaction and collaboration among all involved, based on facilitated communication as well as further evaluation research. We provide examples of several cross-sectorial initiatives that are under way in this area. Finally, we explore some economic aspects of HTE research as part of the drug development, marketing, and treatment process. Understanding the economic incentives present is fundamental to aligning those incentives to improve the availability and utilization of HTE evidence. Clear understandings among regulators, pharma, and payers about high-value targets, methods to efficiently generate and communicate information, and value propositions can lead to "win-win" scenarios for patients, individual payers, the health care system overall, and the future of drug development in producing new medicines.

Keywords: collaborative research, heterogeneity of treatment effect, personalized medicine.

Introduction

As our understanding of the pathophysiology and genetics behind disease and its related therapies has expanded, our appreciation for the variations in effectiveness of different treatments in diverse patient populations has also grown. While heterogeneity of treatment effect (HTE) has been an important element of medical decision making for quite some time, the burgeoning area now often referred to as "personalized medicine" is a more recent phenomenon. It is no longer just the realm of academic researchers interested in the basic science, or those most affected in everyday practice—physicians and their patients. All sectors of the health care world, including policy regulators, payers, and the pharmaceutical, biotech, and medical device industry, are taking a major interest in this expanding field. HTE per se includes both treatments specifically defined by diagnosis using genetic or other biomarker information and more traditional approaches using clinical or phenotypic stratifiers such as demographic characteristics, disease severity, comorbidities, previous response to treatment, side-effect tolerance, behavioral characteristics, and patient/caregiver preferences [1–3]. Improved understanding of HTE is a key enabler of the growth of personalized medicine.

For effective progress in generating and applying evidence about HTE to improve patient care, from the underlying science to frontline practice setting, there needs to be agreement about the type of evidence needed, about methods by which it is generated, evaluated, and communicated, and ultimately about how it is put into practice. There also need to be effective and aligned economic incentives to generate and use that evidence across the health care continuum. The three primary sectors mentioned previously—regulators, payers, and the pharmaceutical, biotech, and medical device industry—are key players in generating, interpreting, and applying HTE-related evidence on a

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large scale, and so it is of much interest to understand how each one views these areas. To that end, a session at the May 2011 ISPOR conference was organized, in which each sector's perspectives were represented and discussed [4]. This article is drawn from the presentations and discussion at that session.

This article is organized into three sections—evidence generation, evidence utilization, and economics. The perspectives of each sector are integrated into each section as appropriate. They are followed by a discussion of selected areas for further consideration and a conclusion.

Evidence Generation

Evidence from clinical trial and related sources

Before a new product is approved, incentives to detect HTE are present but, until fairly recently, have been distinctly muted. From a regulatory perspective, it is well known that using the mean outcome effects from clinical studies does not necessarily paint the full picture of the safety and efficacy profile of the drug, and that using subgroup analysis is one way of identifying HTE [5]. In some cases, the manufacturer may know that delineating subgroup effects is an important way to differentiate the product and wish to see such differentiation recognized in product labeling; when genetic differences in diseases and their treatments are scientifically understood, they can be *prima facie* criteria for differentiation (e.g., HER2, K-ras genetic differences in cancer). Payers often would like to reduce the budget impact of a new product by limiting the population to be treated. Approval bodies such as UK's National Institute for Health and Care Excellence and the German Federal Joint Committee (GBA) have prospective criteria for considering subgroup differences in their review because such differences may affect the cost-effectiveness or relative effectiveness of the product [6].

Important factors, however, work against extensive or exploratory HTE analysis during this preapproval period. Lacking a clear scientific or genetic basis for differentiation, regulatory authorities (e.g., Food and Drug Administration [FDA] and European Medicines Agency) may be skeptical of such claims and prefer to see a product evaluated in the broader population in which it may be used. Manufacturers are more generally inclined to have their products available to larger patient populations unless there are compelling reasons that they need to be limited. In a practical sense, HTE detection often needs large overall sample sizes, but the more patients are included, the more expensive and longer trials become, and analysis of HTE can make submissions more complex both to create and to review. Neither regulatory bodies nor manufacturers are anxious to delay the availability of an effective new product to patients without a good a priori reason that HTE is likely to be present, and so such analysis is often not part of a preagreed development or regulatory review plan. Nevertheless, many manufacturers are now actively investigating HTE potential in early research and development, via genomewide association studies, predictive modeling, and other methods, as a basis for subsequent development planning. In fact, more than 50% of manufacturers have incorporated pharmacogenomics or pharmacogenetic diagnostics into their clinical development programs [7].

Once a product has gone through FDA review and is marketed, the potential to detect HTE improves both due to data availability on product usage and due to the methods that can be applied, especially if different sectors are willing to collaborate in data access and analytic efforts. As more randomized controlled trials (RCTs) are performed, either by the sponsor or by independent researchers, under certain circumstances individual patient data from those trials can be pooled for analyses [8].

While analysis of individual patient data allows for the most detailed analysis of HTE and other comparative effectiveness research questions, access to such data may be quite limited, and the programming and analysis effort is substantial. A more broadly available and classic approach is meta-analysis, and given the increasing number of online journals as well as the results posted on clinicaltrials.gov, the extent of trial results available for meta-analyses is expanding rapidly. Reporting of subgroup results, however, is still quite variable. Uniform guidelines for reporting subgroup results, perhaps defined within disease area, would be helpful, as would guidelines and utilities for interinvestigator cooperation in making unpublished subgroup results available for meta-analyses.

Of course, real-world evidence also begins to accumulate as utilization of the product grows following marketing approval. Such data become a valuable but more analytically challenging source of information on HTE, as discussed in more detail later. Given these different approaches, systematic evidence reviews, such as those sponsored by the Agency for Healthcare Research and Quality, can begin to parse the extant research and refine any conclusions about HTE. The more good quality research is available—a situation that could be enhanced by clear standards for HTE research, whether with RCT or real-world data—the more comprehensive and definitive these reviews can be.

Evidence from real-world data

Real-world evidence demands about the safety, effectiveness, and value associated with biopharmaceutical interventions and devices change as they enter the marketplace. Initially payers, physicians, and other health care providers (HCPs) as well as patients must rely on the evidence of safety and efficacy from the pivotal clinical trials that are available at the time of product launch. Once a product is on the market, however, real-world evidence about the product begins to accumulate rapidly in administrative claims databases, electronic medical record (EMR) systems, and disease and product registries. Real-world data are of great interest to payers, physicians, and manufacturers because it reflect the experiences of patient populations who are treated in actual clinical practice rather than the narrowly defined patient populations studied in clinical trials. Real-world data enable the analysis of variation in medication adherence on health outcomes and health care costs, the analysis of variation in physician treatment patterns, the observation of patient experiences on new treatments as they come on the market, treatment effectiveness in patient groups typically not eligible for clinical trials such as those with multiple comorbid conditions and hence multiple comedications, and many other questions that remain unanswered by RCT.

Databases capturing real-world evidence of health care treatments, outcomes, and utilization enable analysis of large patient populations at relatively low cost and without the delays associated with primary data collection. However, there are well-recognized challenges and limitations with the analysis of these types of observational data that can lead to erroneous conclusions. As data systems evolve and become more integrated, some of these issues will be corrected, as controlling for confounders will be facilitated by the increasing availability of integrated clinical data. For example, the lack of clinical severity measures in medical claims data could be addressed by linking medical claims data with EMRs. In turn, this would address the general lack of health care utilization data across treatment sites typical of most EMR systems. There are several reasons to expect data systems to continue to evolve rapidly over the next several years. For example, in the United States, the Health Information Technology for Economic and Clinical Health Act (February 17, 2009) contained significant economic incentives for providers to adopt meaningful use of EMR systems (as well as penalties if they do not). This is leading to rapid growth in the use of EMRs, which will enhance the technical ability to link EMRs and medical claims data. Similarly, experimentation with new care delivery models

such as accountable care organizations is leading to the creation of health information exchanges that enable the electronic flow of information among provider and payer organizations. These data contain both clinical and health care utilization information.

Even with improvements in data systems, however, the analysis of observational data generally requires the use of sophisticated multivariate statistical methods to draw reliable conclusions. These methods are well established, but best practice regarding the analysis of observational data continues to evolve and results are not as uniformly accepted as randomized controlled clinical trials [9]. Despite the challenges associated with drawing conclusions from observational data, payer organizations rely on such data to review (and sometimes alter) initial coverage and reimbursement decisions, as do regulatory agencies in monitoring product safety.

Unfortunately, data availability, specifically integrated data, can be a significant challenge in generating evidence that payers, physicians, and patients require with respect to treatment safety, effectiveness, and value. In some regions, real-world data do not exist. It is more often the case, however, that the data exist but are not directly accessible. For example, a regional health system within a country may have clinical or claims data on its patients but these data may be accessible only through an academic intermediary. Even when data are available, as with the commercially available medical claims or EMR databases in the United States, they may be incomplete in various ways (e.g., lack information on clinical severity, as well as lack of linkage of claims and EMR data) that create potential biases in drawing inferences from observational data. As a result of these issues, there is interest in developing disease registries in Europe (Innovative Medicines Initiative, see below) and the United States [10,11].

Toward collaboration in evidence generation for HTE

Several efforts to combine individual patient data across data sources are already in progress. The Partnership in Applied Comparative Effectiveness Studies, sponsored by the FDA, is one such project [12]. It combines premarketing data, RCT data submitted to the FDA, with a variety of postmarketing data, such as Medicare, Medicaid, and commercial insurance claims data. Its aim is to provide a comprehensive framework for analyzing HTE as part of comparative effectiveness research, both through combining data sources and through standard and more advanced analytical methods. It is being pursued via a partnership including the Center for Medical Technology Policy, Johns Hopkins University, the Lewin Group, and Buccaneer Computer Systems and Services. Several projects are already under way. The FDA is also involved in a number of other database and analysis projects, including Sentinel, the Medical Device Epidemiological Network, and the Observational Medical Outcomes Partnership [13,14]. Another, purely private sector collaboration has IMS Health partnering with Blue Health Intelligence to build a real-world evidence platform to support epidemiological studies, comparative effectiveness research, safety research, and commercial analytics [15]. In Europe, the Innovative Medicines Initiative supports collaborative research projects and is fostering the development of networks between life science companies and academic experts in Europe with the goal to encourage pharmaceutical innovation in development. It is a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations [16].

Across these efforts, an important goal is to improve detection of HTE in both the benefits and the risks of product use, to identify characteristics of responders versus nonresponders, and to distinguish average versus marginal treatment effects along various patient and risk characteristics [17]. For these goals to be achieved, however, there is much room for improvement in the collection of some less quantifiable outcomes, such as pain, of disease severity measures, as well as less objective but highly informative factors as physician and patient reasons for seeking or prescribing certain treatments. There is also a growing array of methods guidelines to assist researchers when combining diverse data sets, analyzing observational data, or investigating HTE, though the latter in particular is still an emerging field. What is less evident is a consensus on what constitutes transparent and actionable evidence of HTE. FDA standards require "substantial evidence," that is, similar results on primary end points from (generally) two similar RCTs, to make a labeling claim for a pharmaceutical product. The number of times two similar trials with the same end points, however, can be conducted is limited, and practical and statistical considerations limit the number of subgroups that can be compared. Thus, to maximize the opportunities to derive useful HTE evidence from RCTs, joint discussions among regulators, payers, the pharmaceutical industry, as well as with other stakeholders such as clinicians and patients, could be most useful, particularly if conducted during drug development to help specify which patient subpopulations, treatment settings, disease phases, or other aspects would be most important to explore in depth. While regulator-industry consultation is routine, and early industry-payer consultation has become more common of late, more inclusive discussions are still uncommon.

An even more difficult hurdle is establishing necessary and sufficient conditions for actionable HTE evidence from nonrandomized sources, even though these sources have the much larger sample often needed to detect differences across patient types. This is actually more like a triple jump—which data and analysis methods are seen as being of sufficient quality and reliability for research purposes given lack of randomization, in which treatment situations does the benefit-risk situation justify a departure from the usual substantial evidence standard, and when can the various stakeholders agree that the evidence is sufficient for decision purposes? While a top-down, guideline-based approach may be worth pursuing, it also seems that a bottom-up, case-by-case, learn-by-doing approach may have merit. Either way that it is done, there must first be both agreement and commitment from the different stakeholders that generating reliable and actionable evidence on HTE is worth the collaborative effort it will take to do so.

Evidence Utilization

Delivering the right care to the right patient has never been easy, and despite the proliferation of data about patients, treatments, and treatment effects, evidently still has significant hurdles. Health care within the United States has often been delivered without standardized protocols and treatment; in places where treatment protocols or consensus guidelines exist, patients have been shown to not receive the recommended course of therapy across disease areas [18]. With many innovative new therapies (medications, devices, and regimens) becoming available, physicians can have difficulty keeping abreast of the changing standard of care. In addition, changes in the landscape of health care, including increased patient involvement, could presage a change in the nexus of decision making regarding patient care, from physician to group practice in accountable care organizations, or as part of larger centers such as hospital centers, with uncertain effects on consistency and continuity of care from individual physicians.

Despite these challenges to their ability to deliver high-quality care, HCPs (including physicians and other affiliated delivery workers) continue to play the primary caregiver role, with the associated accountability. To deliver such care, HCPs must have access to complete and timely information regarding patient history and current health status, up-to-date treatment protocols and guidelines, and information regarding meaningful patient

outcomes. Biopharmaceutical manufacturers and public and private payers have vested interests in ensuring that these factors are also met to help ensure that the appropriate therapy gets to the patient, at the correct time and in the appropriate setting.

Patients play a larger role in controlling and utilizing the reports of their history, current health status, and treatment outcomes, not only as more informed participants in their interactions with providers but also through participation in social networking health sites. Through social media, patients have the opportunity to track and share their own treatment and outcomes, including reports using standardized patient-reported outcome instruments. These sites promote interactions with other patients, provide suggestions for participation in clinical trials, and, in some cases, even provide summary sheets to take to doctor's appointments [19,20]. Although these data collection sites are outside the traditional health care delivery systems, they represent a source of information useful not only in the individual management of patient care but also as a repository of longitudinal data. Such data could prove useful for identifying new personal elements or even means of data capture that would improve patient care. These methods are currently outside the realm of providers, manufacturers, and payers of health care, but are broadly representative of the changing landscape where information is available in a more timely, broad-based, and relatively uncontrolled manner. While current efforts focus primarily on linking claims databases and EHR, future activities should expand to include these valuable patient-centric data sources, to provide a 360-degree perspective of health care delivery and outcomes and enable more complete evidence utilization during diagnosis and treatment.

Medication adherence is a good example of a behavioral characteristic that differs by patient and can be fairly easily tracked (i.e., refills); if such information is well utilized by providers and payers, patient outcomes could be improved. Certain patient characteristics (income/insurance, "healthy adherer" profile, previous adherence, disease severity) can be used to better predict general adherence issues; product side-effect profiles and co-pays (relative to other medications) may predict specific product adherence; prescription refill data can identify ongoing adherence. Such evidence can be used by the provider to engage the patient about medication problems or other adherence issues, and perhaps lead to alternative medication choices. Payers can potentially use their data to understand adherence determinants in their own population —particularly sensitivities to co-pays—and design their programs to better incentivize utilization of the appropriate medication in the appropriate patient.

Darkow et al. [21] provide an illustration of how adherence data have been utilized to improve treatment and outcomes [21]. In a study of the use of imatinib (Gleevec®) for the treatment of chronic myelogenous leukemia, the authors found that mean total health care costs for patients with low medication possession ratios (under 50%) were $131,357—more than three times the expenditures of patients with medication possession ratios of 90% or higher. UnitedHealthcare has reported that they established a program to reach out to physicians of patients with chronic myelogenous leukemia to assess the appropriateness of treating these patients with imatinib. Simultaneously, patients were contacted to help promote imatinib medication adherence. In general, improved medication adherence is an area of common interest among all health care stakeholders. The imatinib example illustrates that this can be the case even when the treatment itself is associated with significant health care expenditure.

Technology to facilitate interactions among patients, physicians, and other HCPs is advancing rapidly. Nearly all health plans now have Web sites that facilitate submission of claims for reimbursement, as well as interactions between patients and their physicians. Increasingly, applications for these same capabilities are being developed for handheld devices. As these technological developments continue to advance, the communication pathways among payers, patients, and physicians should continue to expand.

Combining evidence generation and utilization: Collaborations involving real-world data

A number of collaborations have formed to support not only evidence generation but also utilization with respect to the clinical effectiveness, safety, and value associated with pharmacotherapies and other health care interventions. These are partnerships among organizations to combine data assets and/or analytics to generate actionable insights. They include the following:

- Optum has announced the formation of Optum Labs, an organization that is intended to be a collaboration among various stakeholders (integrated delivery networks, private and government payers, life sciences companies, academic institutions, etc.) to tackle major health care problems. Optum Labs, modeled after Bell Labs, the research and development wing of AT&T, will provide a secure data environment, access to a wide variety of health care datasets, high-speed computing and analytics, and deep expertise in statistical analysis of observational data [22].
- Wellpoint and IBM Watson are partnering to explore the ability to provide physicians with evidence-based diagnosis and treatment recommendations at the point of care on the basis of clinical data, evidence from available research, and other sources. This effort is an attempt to examine whether the artificial intelligence and high-speed computing capabilities of IBM Watson can be effectively applied in the health care space [23]. At the other end of the spectrum, Archimedes is an extremely sophisticated mathematical model that attempts to simulate interactions among human physiology, disease, interventions, and health care systems [24].
- There are several examples of health plan collaborations with research organizations and biopharmaceutical companies. One of the first of such partnerships was formed by Wellpoint, its research arm HealthCore, and AstraZeneca to create a real-world evidence and analytics platform to support evidence generation to better understand treatment effectiveness, safety, and value of existing therapies. This platform is also being used to support the development of new therapies through a better understanding of the natural history of disease and where current therapies fall in the treatment continuum [23]. Similarly, Competitive Health Analytics (a wholly owned subsidiary of Humana) has entered into a 5-year partnership with—among others—Pfizer to design and execute a research agenda focused primarily on the delivery of health care to seniors [25].
- Quintiles and Allscripts have a strategic partnership to use the Allscripts electronic health record to develop software tools to facilitate drug development [26].

Ultimately, all these partnerships reflect the realization that it is futile to attempt to corner the market on data. Data are necessary, but not sufficient, for generating evidence that can then be utilized in the real world. To answer the questions posed by payers, regulators, providers, and patients, data sets need to be constructed that contain the *relevant* variables typically from *integrated* data sources. Bigger is not necessarily better if key variables are missing. Finally, appropriate methodologies need to be utilized. The need to merge different types of data (e.g., claims data with electronic clinical data, EMR, and tumor registry information), as well as have access to the methodological expertise to properly analyze the data, is a stimulus for many of the collaborations.

Although engaged in data generation for registration of medicinal products, biopharmaceutical companies conduct prospective observational disease registries of real-world clinical practice that could inform treatment protocols and guidelines. An example of this is the National Registry of Myocardial Infarction, initially sponsored as a postapproval safety study for Genentech. Over time, the National Registry of Myocardial Infarction became a repository that not only informed clinicians regarding the standard of care but actually drove important changes that shortened time to care and improved patient outcomes [27]. Yet challenges remain in bringing all vested parties to the table to discuss studies that would ultimately benefit patient outcomes. The relevant design and data interpretation contributions are not always included in these large-scale research projects, which ultimately limits the application of the evidence generated. Also, research sponsorship can lead to perception of bias in design and analysis, which minimizes the impact in presentation of results. Academic and governmental entities conducting federally funded research face some requirements to ensure transparency with regard to design, conduct, and interpretation of results. Parties with a perceived vested interest in the outcomes of studies they conduct (i.e., biopharma, private payer, care centers) are increasingly imposing their own reporting standards and have recently begun to address external calls for transparency (beyond regulatory submissions), which may address the perception of deficiencies in methodology and biased conclusions [28,29]. Collaborations, such as those between industry and payers, can help mitigate concerns about transparency. They could also improve analytic methods and reporting that some feel taints unilaterally conducted research; ultimately, this could lead to more rapid application of the results.

Economics

Properly implemented, HTE has the potential to improve efficiency of care while still providing incentives for drug development and reimbursement, but economic considerations play an important role in decisions about evidence generation and utilization. From a pharmaceutical industry perspective, HTE evidence, almost by definition, is likely to target a treatment to a smaller set of patients and thus limit the market size. As such one can model how it would shift the product's demand curve to the left, or make it steeper, or perhaps kink it or alter it in some other fashion. In any case, the limited market size generally becomes an important issue in drug development decisions in the pharmaceutical industry. Drug development decisions are based in part on the expected rate of return to investments in research, which, in turn, is determined largely by expected revenues versus development costs. To achieve revenues that justify investment, reduced quantities sold may need to be offset by higher prices and/or lower costs. Higher prices may be justified because of the greater effectiveness expected from more targeted treatments, though the elasticity of demand and/or cost-effectiveness here may or may not be consistent with pricing that would yield a reasonable return on investment, and other payer-based considerations around pricing will come into play [30]. Reduction of development costs may be feasible if identification of patients most likely to respond to a given treatment can be done early enough to reduce trial sizes and increase the probability of success during phase 3, given agreement to this strategy by regulators. The need for development of companion diagnostics would introduce other economic considerations, both commercially and for HTA purposes [31]. Better identification of the most appropriate patients for treatment may also hasten diffusion of the product to the target population, thus moving revenues forward in time and increasing their net present value. All these factors and more will influence industry decisions about evidence generation during drug development as well as post-launch, from go/no-go decisions to the nature and size of clinical trials.

From the payer's perspective, economics plays a role in utilizing evidence supporting personalized medicine on at least two fronts as well. In terms of the price of the treatment per se, willingness to pay is heavily influenced by the impact of the treatment on the overall episode of care cost. As illustrated by the Gleevec example noted earlier, commercial payers can certainly be motivated to cover (and even encourage) therapies that lower the total cost of an episode of care for targeted individuals—even when such therapies are, themselves, very expensive. Also important are the transaction costs of identifying the target population in daily practice—not only any needed testing but also the costs of educating physicians about such heterogeneity and making the relevant patient information available to the physician in real time, and possibly building some checks into the reimbursement system. As electronic health information systems improve, patient-specific treatment approaches become much more feasible, but are still not costless. Payers may also find that implementing patient-specific treatment approaches can change the uncertainty around patient outcomes— uncertainty could increase if the evidence base is thinner than usual label-based evidence or decrease if the targeted treatments truly work better. Thus, changes to financial risk due to the uncertainty may need to be considered, while not discounting an ethical or humanistic risk that may be incurred as well. If there is a concern about increased risk, real-time monitoring of outcomes and costs could be used to trigger stop or continuation decisions, but this would incur costs as well. The kinds of partnerships of payers with industry or other businesses discussed above can help to improve cost-efficiency, distribute the cost burden, or reduce the business decision-related uncertainty that can be economic obstacles to utilizing HTE evidence in managing patient care.

Regulators can significantly influence the economics of HTE in several ways. From their perspective, reductions in sample size to target certain populations, even if sensible for efficacy determination, may be less desirable for provision of the safety database. Because a drug can legally be prescribed for almost any patient by a physician once it is approved, regulators prefer to have a large and broad safety database before a drug is approved, depending on the perceived benefit-risk profile of the product. In addition, some of the more innovative and potentially efficient trial designs, for example, Bayesian adaptive designs, have proven acceptable in phase 2 dose-finding studies but have been deemed less suitable for pivotal phase 3 trials; choice of prior is one issue here. The FDA has given guidance, however, for the use of Bayesian approaches for medical devices [31]. In cases of HTE determination by companion diagnostics, requirements for joint testing of diagnostics and therapeutics can influence the design and cost of clinical trials as well as the business relationships between the test and therapy manufacturers [7,32].

Finally, the economics of this situation, that is, the risk-reward of generating new evidence, such as on HTE, from which other parties can benefit, has been approached in a game-theoretic, decision analysis sense [33]. Another, better known, approach is that generated by value of information considerations [34]. In both cases, there can be returns to society from incremental health care evidence that transcend the economic return to an individual party funding the research. While risk-sharing agreements and coverage-with-evidence development agreements are becoming more common between industry and payers, there is certainly still potential to exploit these mechanisms to incentivize the generation and utilization of HTE evidence. Alternatively, government-based mechanisms to generate the socially optimal amount of evidence may be more practical in some situations, further supporting the

other reasons for communication and collaboration across stakeholders discussed above.

Conclusions

Across the three realms of evidence generation, evidence utilization, and economics that we have discussed, it is clear that any given stakeholder acting individually may neither have sufficient incentive nor the resources necessary to properly pursue the study of HTE for new products and use those results in the treatment of patients. Collaborative efforts across these stakeholders to optimize all types of evidence generation have begun and are likely to be synergistic, but challenges in the collection of good outcomes data and interpretation of nonrandomized data remain. Given some consensus on what constitutes reliable evidence, better information systems that communicate well with providers and patients can then play an important role in utilizing evidence on HTE to optimize individual patient treatments—true "personalized medicine." More efficiency in evidence generation and utilization, as well as the clinical benefit and long-term cost savings from more targeted and effective treatments, should help balance the economic factors involved in developing and implementing such treatments. Clear understandings among regulators, pharma, and payers about high-value targets, methods to efficiently generate and communicate information, and value propositions can lead to "win-win" scenarios for patients, individual payers, the health care system overall, and the future of drug development in producing new medicines.

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REFERENCES

[1] President's Council of Advisors on Science and Technology. Priorities for Personalized Medicine. Washington, DC: President's Council of Advisors on Science and Technology, 2008.

[2] Kravitz RL, Duan N, Breslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. Milbank Q 2004;82:661–87.

[3] Redekop K, Mladsi D. The faces of personalized medicine: a framework for understanding its meaning and scope. Value Health 2013;16(Suppl.): S4–9.

[4] ISPOR Institutional Council Comparative Effectiveness Research Working Group. "Differences on differences: does perspective matter when considering heterogeneity of treatment effect?" ISPOR Forum at the ISPOR 15th Annual International Meetings, May 2011; Baltimore, MD.

[5] US Food and Drug Administration. Guidance for Industry: E9 Statistical Principles for Clinical Trials. Washington, DC: U.S. Department of Health and Human Services, September 1998.

[6] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. London, UK: National Institute for Health and Care Excellence, June 2008. Available from: http://www.nice.org.uk/media/b52/a7/tamethodsguideupdatedjune2008.pdf. [Accessed April 22, 2013].

[7] Faulkner E, Annemans L, Garrison L, et al. Challenges in the development and reimbursement of personalized medicine—payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR Personalized Medicine Special Interest Group. Value Health 2012;15:1162–71.

[8] Ashley P, Jones AP, Riley RD, et al. Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. Clinical Trials 2009;6:16–27.

[9] Johnson M, Crown W, Martin B, et al. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from non-randomized studies of treatment effects using secondary data sources: report of the ISPOR Retrospective Database Analysis Task Force—part III. Value Health 2009;12:1062–73.

[10] Dreyer N, Garner S. Registries for Robust Evidence. JAMA 2009;302:790–1.

[11] NIH Genetic Testing Registry. Available at: http://www.NCBI.NLM.NIH.GOV/GTR. [Accessed April 18, 2013].

[12] Food and Drug Administration. Partnership in Applied Comparative Effectiveness Science (PACES), 2010. Available from: https://www.fbo.gov/index?s=opportunity&mode=form&tab=core&id=;118a867ca5850ebbcd3a06961355b285&_cview=0. [Accessed March 2, 2012].

[13] Food and Drug Administration. Medical Device Epidemiology Network Initiative (MDEpiNet). Available from: http://www.fda.gov/MedicalDevices/ScienceandResearch/EpidemiologyMedicalDevices/MedicalDeviceEpidemiologyNetworkMDEpiNet/default.htm. [Accessed April 18, 2013].

[14] Observational Medical Outcomes Partnership. Available from: http://omop.org/. [Accessed April 18, 2013].

[15] IMS to combine largest U.S. health plan claims database with IMS LifeLink, enabling innovative patient treatment insights [press release]. Parsippany, NJ: IMS; September 12, 2012. Available from: http://www.imshealth.com/portal/site/ims/menuitem.d248e29c86589c9c30e81c033208c22a/?vgnextoid=9a192b2b52cb9310VgnVCM10000076192ca2RCRD&vgnextchannel=437879d7f269e210VgnVCM10000071812ca2RCRD. [Accessed April 18, 2013].

[16] Innovative Medicines Initiative. Available from: www.imi.europa.eu. [Accessed April 18, 2013].

[17] Heckman JJ, Vytlacil E. Structural equations, treatment effects and econometric policy evaluation. Econometrica 2005;73:669–738.

[18] McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;48:635–45.

[19] PatientsLikeMe. Available from: http://www.patientslikeme.com/. [Accessed April 18, 2013].

[20] 23andme. Available from: https://www.23andme.com/. [Accessed April 18, 2013].

[21] Darkow T, Henk H, Thomas S, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. Pharmacoeconomics 2007;25:481–96.

[22] Optum, Mayo Clinic partner to launch Optum Labs: an open, collaborative innovation facility focused on better care for patients [press release]. Cambridge, MA: Mayo Clinic; January 15, 2013. Available from: http://online.wsj.com/article/PR-CO-20130115-904295.html?mod=crnews. [Accessed August 15, 2013].

[23] Fierce Health Payer. WellPoint taps IBM's Watson to diagnose, recommend treatment. Available from: http://www.fiercehealthpayer.com/story/wellpoint-taps-ibms-watson-diagnose-recommend-treatment/2011-09-16. [Accessed April 18, 2013.].

[24] Archimedes Inc. Archimedes Model. Available from: http://www.archimedesmodel.com. [Accessed April 18, 2013].

[25] Humana and Pfizer form research partnership to improve health care delivery for seniors [press release]. Louisville, KY: Pfizer; October 13, 2011. Available from: http://www.businesswire.com/news/home/20111013006441/en/Humana-Pfizer-Form-Research-Partnership-Improve-Health. [Accessed April 18, 2013].

[26] Fierce Biotech IT. Quintiles, Allscripts to tap health IT data for drug research. Available from: http://www.fiercebiotechit.com/story/quintiles-allscripts-tap-health-it-data-drug-research/2012-07-16. [Accessed April 18, 2013].

[27] French WJ, Reddy VS, Barron HV. Transforming quality of care and improving outcomes after acute MI: lessons from the National Registry of Myocardial Infarction. JAMA 2012;308:771–2.

[28] Herper M. With transparency pledge, Glaxo makes promises no other drug company has. Forbes Online Oct 11, 2012. Available from: http://www.forbes.com/sites/matthewherper/2012/10/11/with-transparency-pledge-glaxo-makes-promises-no-other-drug-company-has/. [Accessed April 22, 2013].

[29] BBC News Health. Roche agrees to release all trial data on Tamiflu drug. April 5, 2013. Available from: http://www.bbc.co.uk/news/health-22029708. [Accessed April 22, 2013].

[30] Payne K, Annemans L. Reflections on market access for personalized medicine: recommendations for Europe. Value Health 2013;16 (Suppl.): S32–8.

[31] US Food and Drug Administration. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. Centers for Devices and Radiological Health. Updated February 5, 2010. Available from: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm. [Accessed April 18, 2013].

[32] US Food and Drug Administration. Draft guidance for industry and Food and Drug Administration staff: in vitro companion diagnostic devices. July 14, 2011. Available from: http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm. [Accessed April 18, 2013].

[33] Mansley EC, Elbasha EH, Teutsch SM, Berger ML. The decision to conduct a head-to-head comparative trial: a game-theoretic analysis. Med Decis Making 2007;27:364–79.

[34] Basu A, Meltzer DW. Value of information on preference heterogeneity and individualized care. Med Decis Making 2007;27:112.